09/800660 (5060)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 January 2001 (08.01.01)	
International application No. PCT/SE00/00846	**Applicant's or agent's file reference** H 2155-1 WO
International filing date (day/month/year) 03 May 2000 (03.05.00)	**Priority date** (day/month/year) 03 May 1999 (03.05.99)
Applicant LINSCHOTEN, Marcel et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 October 2000 (26.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Leitao
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

09/600660

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
H 2155-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/00846	03.05.2000	03.05.1999
International Patent Classification (IPC) or national classification and IPC7		
C 07 F 9/38		
Applicant		
AstraZeneca AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.10.2000	19.06.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Telex 17978 PATOREG-S
Authorized officer Göran Karlsson/BS Telephone No. 08-782 25 00	

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/00846

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/00846

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☒ the entire international application,

☐ claims Nos. _____

because:

☒ the said international application, or the said claims Nos. 16-17
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

A method for treatment of the human or animal body by therapy (PCT Rule 67.1 (iv)).

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-15
are so unclear that no meaningful opinion could be formed *(specify)*:

The present claims 1-15 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. No special search effort can be made for searching unduly wide and speculative claims (PCT Search Guidelines C-III 3.7).

.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds prepared in the examples.

The applicants attention is drawn to the fact that claims relating to inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/00846

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement **f. Box V.2.**

Novelty (N)	Claims		YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims		NO
Industrial applicability (IA)	Claims		YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The present claims 1-15 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. No special search effort can be made for searching unduly wide and speculative claims (PCT Search Guidelines C-III 3.7).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds prepared in the examples. No such compound has been found.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* H 2155-1 WO

Box No. I TITLE OF INVENTION

NEW COMPOUNDS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AstraZeneca AB
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

State *(that is, country)* of nationality:
SE

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LINSCHOTEN, Marcel
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
NL

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Global Intellectual Property, Patents
AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Sheet No. 2

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

POLLA, Magnus
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AL** Albania
☒ **AM** Armenia
☒ **AT** Austria
☒ **AU** Australia
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina
☒ **BB** Barbados
☒ **BG** Bulgaria
☒ **BR** Brazil
☒ **BY** Belarus
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China
☒ **CR** Costa Rica
☒ **CU** Cuba
☒ **CZ** Czech Republic
☒ **DE** Germany
☒ **DK** Denmark
☒ **DM** Dominica
☒ **EE** Estonia
☒ **ES** Spain
☒ **FI** Finland
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia
☒ **GH** Ghana
☒ **GM** Gambia
☒ **HR** Croatia
☒ **HU** Hungary
☒ **ID** Indonesia
☒ **IL** Israel
☒ **IN** India
☒ **IS** Iceland
☒ **JP** Japan
☒ **KE** Kenya
☒ **KG** Kyrgyzstan
☒ **KP** Democratic People's Republic of Korea
☒ **KR** Republic of Korea
☒ **KZ** Kazakhstan
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco
☒ **MD** Republic of Moldova
☒ **MG** Madagascar
☒ **MK** The former Yugoslav Republic of Macedonia
☒ **MN** Mongolia
☒ **MW** Malawi
☒ **MX** Mexico
☒ **NO** Norway
☒ **NZ** New Zealand
☒ **PL** Poland
☒ **PT** Portugal
☒ **RO** Romania
☒ **RU** Russian Federation
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia
☒ **SK** Slovakia
☒ **SL** Sierra Leone
☒ **TJ** Tajikistan
☒ **TM** Turkmenistan
☒ **TR** Turkey
☒ **TT** Trinidad and Tobago
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine
☒ **UG** Uganda
☒ **US** United States of America
☒ **UZ** Uzbekistan
☒ **VN** Viet Nam
☒ **YU** Yugoslavia
☒ **ZA** South Africa
☒ **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ DZ Algeria
☒ AG Antigua and Barbuda

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn bythe applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 03 May 1999 (03.05.1999)	9901572-9	Sweden (SE)		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA / SE

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date (day/month/year)	Number	Country (or regional Office)
4 February 2000	SE99/00527	Sweden (SE)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 48
claims	: 9
abstract	: 1
drawings	:
sequence listing part of description	:
Total number of sheets	: 62

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: GF1189/2000
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: ITS Report SE99/00527

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje, 03 May 2000

Christer Wahlström

Christer Wahlström
Global Intellectual Property, Patents, AstraZeneca AB

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H 2155-1 WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE00/00846	International filing date *(day/month/year)* 03.05.2000	Priority date *(day/month/year)* 03.05.1999
International Patent Classification (IPC) or national classification and IPC7 C 07 F 9/38		
Applicant AstraZeneca AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

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   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26.10.2000	19.06.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Telex 17978 PATOREG-S	Authorized officer Göran Karlsson/BS Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/00846

I. Basis of the report

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pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

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pages _____, as originally filed
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pages _____, filed with the letter of _____

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pages _____, filed with the demand
pages _____, filed with the letter of _____

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pages _____, as originally filed
pages _____, filed with the demand
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2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

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☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

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4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

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** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/00846

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☒ the entire international application,

☐ claims Nos. _____

because:

☒ the said international application, or the said claims Nos. 16-17
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

A method for treatment of the human or animal body by therapy (PCT Rule 67.1 (iv)).

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-15
are so unclear that no meaningful opinion could be formed *(specify)*:

The present claims 1-15 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. No special search effort can be made for searching unduly wide and speculative claims (PCT Search Guidelines C-III 3.7).

.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds prepared in the examples.

The applicants attention is drawn to the fact that claims relating to inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement **cf. Box V.2.**

Novelty (N)	Claims		YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims		NO
Industrial applicability (IA)	Claims		YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The present claims 1-15 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. No special search effort can be made for searching unduly wide and speculative claims (PCT Search Guidelines C-III 3.7).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds prepared in the examples. No such compound has been found.

09600660

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(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

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(75) Inventors/Applicants *(for US only)*: LINSCHOTEN, Marcel [NL/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). POLLA, Magnus [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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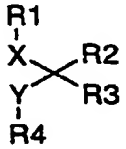
WO 00/66550 A1

(54) Title: NEW COMPOUNDS



(I)

(57) Abstract: The present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts, which compounds inhibit carboxypeptidase U and thus can be used in the prevention and treatment of diseases associated with carboxypeptidase U. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
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A1

(11) International Publication Number: WO 00/66550

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LINSCHOTEN, Marcel [NL/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). POLLA, Magnus [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

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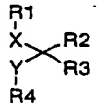
(54) Title: NEW COMPOUNDS



(I)

(57) Abstract

The present invention relates to compounds of Formula (I), and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts, which compounds inhibit carboxypeptidase U and thus can be used in the prevention and treatment of diseases associated with carboxypeptidase U. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

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EE	Estonia	LR	Liberia	SG	Singapore		

NEW COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to novel compounds, and pharmaceutically acceptable salts thereof, which inhibit basic carboxypeptidases, more specifically carboxypeptidase U, and thus can be used in the prevention and treatment of diseases wherein inhibition of carboxypeptidase U is beneficial. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

BACKGROUND OF THE INVENTION

Fibrinolysis is the result of a series of enzymatic reactions resulting in the degradation of fibrin by plasmin. The activation of plasminogen is the central process in fibrinolysis. The cleavage of plasminogen to produce plasmin is accomplished by the plasminogen activators, tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Initial plasmin degradation of fibrin generates carboxy-terminal lysine residues that serves as high affinity binding sites for plasminogen. Since plasminogen bound to fibrin is much more readily activated to plasmin than free plasminogen this mechanism provides a positive feedback regulation of fibrinolysis.

One of the endogenous inhibitors to fibrinolysis is carboxypeptidase U (CPU). CPU is also known as plasma carboxypeptidase B. active thrombin activatable fibrinolysis inhibitor (TAFIa), carboxypeptidase R and inducible carboxypeptidase activity. CPU is formed during coagulation and fibrinolysis from its precursor proCPU by the action of proteolytic enzymes *e.g.* thrombin, thrombin-thrombomodulin complex or plasmin. CPU cleaves basic amino acids at the carboxy-terminal of fibrin fragments. The loss of carboxy-terminal lysines and thereby of lysine binding sites for plasminogen then serves to inhibit fibrinolysis.

By inhibiting the loss of lysine binding sites for plasminogen and thus increase the rate of plasmin formation, effective inhibitors of carboxypeptidase U would be expected to facilitate fibrinolysis.

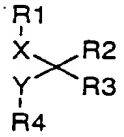
2-mercaptomethyl-3-guanidinoethylthiopropanoic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Hendriks, D. *et al.*, Biochimica et Biophysica Acta, 1034 (1990) 86-92.

Guanidinoethylmercaptosuccinic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Eaton, D. L., *et al.*, The Journal of Biological Chemistry, 266 (1991) 21833-21838.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the Formula I are particularly effective as inhibitors of carboxypeptidase U and thereby useful as medicaments for the treatment or profylaxis of conditions wherein inhibition of carboxypeptidase U is beneficial.

In one aspect, the invention thus relates to compounds of the general Formula I,



(I)

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R_1 represents,

C_1-C_6 alkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

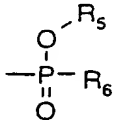
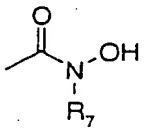
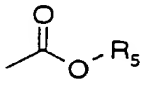
heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

or aryl, substituted with one or more basic groups such as amino, amidino and/or guanidino,

R_2 represents H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, Z_2N-CO-O-, ZO-CO-NZ- or Z_2N-CO-NZ- group,

R_3 represents $COOR_5$, $SO(OR_5)$, SO_3R_5, $P{=}O(OR_5)_2$, $B(OR_5)_2$, $P{=}OR_5(OR_5)$, or tetrazole, or any carboxylic acid isostere,

R_4 represents a  -group, or a  -group, or a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_6 represents C_1-C_6 alkyl, aryl, cycloalkyl, heterocyclyl, or an optionally N-substituted H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group,

R_7 represents H or C_1-C_6 alkyl,

X represents O, S, SO, SO_2, $C(Z)_2$, N(Z), NR_7SO_2, SO_2NR_7, NR_7CO or $CONR_7$,

Y represents O, N(Z), S, $C(Z)_2$, or a single bond,

Z represents independently H, C_1-C_6 alkyl, aryl, cycloalkyl or heterocyclyl,

with the proviso that when X represents O, S, SO, SO_2, N(Z), NR_7SO_2, SO_2NR_7, or NR_7CO then Y represents $C(Z)_2$ or a single bond.

Preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R_1 represents,

C_1-C_6 alkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

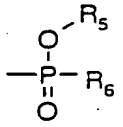
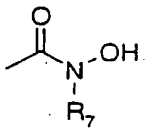
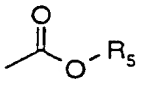
heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

or aryl, substituted with one or more basic groups such as amino, amidino and/or guanidino,

R_2 represents H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, Z_2N-CO-O-, ZO-CO-NZ- or Z_2N-CO-NZ- group,

R_3 represents $COOR_5$,

R_4 represents a  -group, or a  -group, or a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_6 represents C_1-C_6 alkyl, aryl, cycloalkyl, heterocyclyl, or an optionally N-substituted H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group,

R_7 represents H or C_1-C_6 alkyl,

X represents $C(Z)_2$,

Y represents O, N(Z), S, $C(Z)_2$, or a single bond,

Z represents independently H, C_1-C_6 alkyl, aryl, cycloalkyl or heterocyclyl.

More preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R_1 represents,

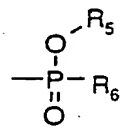
cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

R_2 represents H, C_1-C_3 alkyl, amino, halogen or hydroxy,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_6 represents C_1-C_6 alkyl, aryl, cycloalkyl, heterocyclyl, or an optionally N-substituted H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group,

X represents $C(Z)_2$,

Y represents O or $C(Z)_2$,

Z represents independently H or C_1-C_6 alkyl.

Other more preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R_1 represents,

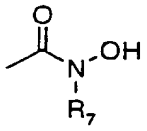
cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

R_2 represents H, C_1-C_3 alkyl, amino, halogen or hydroxy,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_7 represents H or C_1-C_6 alkyl,

X represents $C(Z)_2$,

Y represents $C(Z)_2$ or a single bond,

Z represents independently H or C_1-C_6 alkyl.

Yet other more preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R_1 represents,

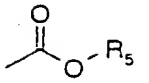
cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

R_2 represents H, C_1-C_3 alkyl, amino, halogen or hydroxy,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

X represents $C(Z)_2$,

Y represents $C(Z)_2$ or a single bond,

Z represents independently H or C_1-C_6 alkyl.

Even more preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

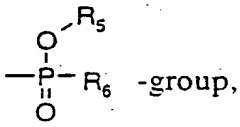
R_1 represents,

cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

R_2 represents H, F, C_1 alkyl,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_6 represents C_1-C_6 alkyl, aryl, cycloalkyl, heterocyclyl, or an optionally N-substituted H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group,

X represents $C(Z)_2$,

Y represents O or $C(Z)_2$,

Z represents independently H or C_1-C_6 alkyl.

Other even more preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

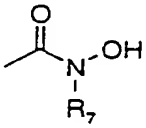
R_1 represents,

cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

R_2 represents H, F, C_1 alkyl,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_7 represents H or C_1-C_6 alkyl,

X represents $C(Z)_2$,

Y represents $C(Z)_2$ or a single bond,

Z represents independently H or C_1-C_6 alkyl.

Yet other even more preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

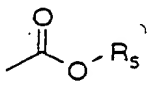
R_1 represents,

cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

R_2 represents H, F, C_1 alkyl,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

X represents $C(Z)_2$,

Y represents $C(Z)_2$ or a single bond,

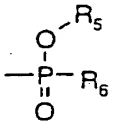
Z represents independently H or C_1-C_6 alkyl.

Most preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R_1 represents pyridyl or piperidinyl,

R_2 represents H,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H,

R_6 represents C_1-C_6 alkyl or an optionally N-substituted H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group,

X represents CHZ,

Y represents CHZ,

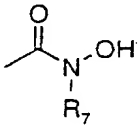
Z represents independently H or C_1-C_6 alkyl.

Other most preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R_1 represents pyridyl or piperidinyl,

R_2 represents H,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H,

R_7 represents H,

X represents CHZ,

Y represents CHZ or a single bond,

Z represents independently H or C_1-C_6 alkyl.

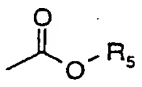
Yet other most preferred compounds according to the present invention are those of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R_1 represents pyridyl or piperidinyl,

R_2 represents H,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H,

X represents CHZ,

Y represents CHZ or a single bond,

Z represents independently H or C_1-C_6 alkyl.

The following definitions shall apply throughout the specification and the appended claims:

The term "basic group" denotes a basic group, wherein the conjugate acid of said basic group has a pKa of from about –5 to about 25, preferably of from 1 to 15.

The term "carboxylic acid isostere" denotes an acidic group having a pKa of from about –5 to about 25, preferably of from 1 to 15.

The term "C_1–C_6 alkyl" denotes a straight or branched, saturated or unsaturated, substituted or unsubstituted alkyl group having 1 to 6 carbon atoms in the chain wherein the alkyl group may optionally be interrupted by one or more heteroatoms selected from O, N or S. Examples of said alkyl include, but is not limited to, methyl, ethyl, ethenyl, ethynyl, n-propyl, iso-propyl, propenyl, iso-propenyl, propynyl, n-butyl, iso-butyl, sec-butyl, t-butyl, butenyl, iso-butenyl, butynyl and straight- and branched-chain pentyl and hexyl.

The term "C_1–C_3 alkyl" denotes a straight or branched, saturated or unsaturated, substituted or unsubstituted alkyl group having 1 to 3 carbon atoms in the chain wherein the alkyl group may optionally be interrupted by one or more heteroatoms selected from O, N or S. Examples of said alkyl include, but is not limited to, methyl, ethyl, ethenyl, ethynyl, n-propyl, iso-propyl, propenyl, iso-propenyl, propynyl.

The term "C_1 alkyl" denotes a substituted or unsubstituted alkyl group having 1 carbon atom. An example of said alkyl include, but is not limited to, methyl,

The term "C_1-C_6 alkoxy" denotes an alkyl-O-group, wherein C_1-C_6 alkyl is as defined above.

The term "C_1-C_3 alkoxy" denotes an alkyl-O-group, wherein C_1-C_3 alkyl is as defined above.

The term "heterocyclyl" denotes a substituted or unsubstituted, 4- to 10- membered monocyclic or multicyclic ring system in which one or more of the atoms in the ring or rings is an element other than carbon, for example nitrogen, oxygen or sulfur, especially 4-, 5- or 6-membered aromatic or alifatic hetorocyclic groups, and includes, but is not limited to azetidine, furan, thiophene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxathiolane, oxazolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isoxazole, isothiazole, oxadiazole, furazan, triazole, thiadiazole, pyran, pyridine, piperidine, dioxane, morpholine, dithiane, oxathiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, thiadiazine, dithiazine, azaindole, azaindoline,

indole, indoline, naphthyridine groups, and shall be understood to include all isomers of the above identified groups. The term "azetidinyl" shall for example by understood to include the 2-, and 3-isomers and the terms "pyridyl" and "piperidinyl" shall for example by understood to include the 2-, 3-, and 4-isomers.

The term "cycloalkyl" denotes a saturated or unsaturated, substituted or unsubstituted, non-aromatic ring composed of 3, 4, 5, 6 or 7 carbon atoms, and includes, but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclopentadienyl, cyclohexadienyl and cycloheptadienyl groups,

The term "halogen" includes fluoro, chloro, bromo and iodo groups.

The term "aryl" denotes a substituted or unsubstituted C_6-C_{14} aromatic hydrocarbon and includes, but is not limited to, phenyl, naphthyl, indenyl, antracenyl, fenantrenyl, and fluorenyl.

The term "aryloxy" denotes an aryl-O-group, wherein aryl is as defined above.

The term "acyl" denotes an alkyl-CO-group, wherein alkyl is as defined above.

The term "aroyl" denotes an aryl-CO-group, wherein aryl is as defined above.

The term "alkylthio" denotes an alkyl-S-group, wherein alkyl is as defined above.

The term "arylthio" denotes an aryl-S-group, wherein aryl is as defined above.

The term "aroylamino" denotes an aroyl-N(Z)-group, wherein aroyl and Z is as defined above.

The term "acylamino" denotes an acyl-N(Z)-group, wherein acyl and Z is as defined above.

The term "carbamoyl" denotes a H_2N-CO-group.

The term "alkylcarbamoyl" denotes a Z_2N-CO-group wherein Z is as defined above.

The term "substituted" denotes an "C_1 alkyl", "C_1-C_3 alkyl", "C_1-C_6 alkyl", "cycloalkyl", "heterocyclyl", "aryl", H_2N-C(Z)-CONH-C(Z)- or a H_2N-C(Z)- group as defined above which is substituted by one or more acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, thio, Z_2N-CO-O-, ZO-CO-NZ-, or Z_2N-CO-NZ- groups.

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the present invention. It should also be understood that all the diastereomeric forms possible are within the scope of the invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of Formula I, such as prodrugs.

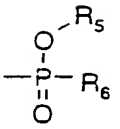
Depending on the process conditions the compounds of Formula I are obtained either in neutral or salt form or as a solvate, e.g. a hydrate, and are all within the scope of the present invention.

Preparation

The present invention also provides the process A-C for the manufacture of compounds with the general Formula I.

Process A

Process A for manufacture of compounds with the general Formula I, wherein R_1, R_5, R_6, and Z are as defined above and R_2 is H, R_3 is $COOR_5$,

R_4 represents a  -group,

X is $C(Z)_2$, Y is $C(Z)_2$ and comprises the following steps:

a) Compounds of the general Formula II,

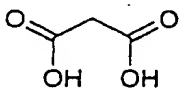
$$R1—X-OH \qquad (II)$$

wherein R_1 and Z is as defined for Formula I and X is $C(Z)_2$, which are either commercially available or are available using known techniques, can be converted into a compound of the general Formula III,

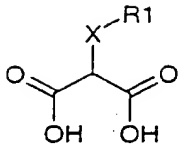
$$R1—X-L \qquad (III)$$

wherein L is a suitable leaving group, such as a chloro, bromo, iodo, triflate or tosyl group, under standard conditions using a suitable reagent, such as PPh_3/CBr_4, TosCl/pyridine or $(CF_3SO_2)_2O$/TEA).

b) Compounds of the general Formula III can thereafter be reacted with compounds of the general Formula IV,

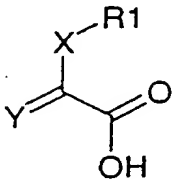
 (IV)

which are either commercially available or are available using known technics, in the presence of a suitable base, such as K_2CO_3 or NaH, under standard conditions to give compounds of the general Formula V,



(V)

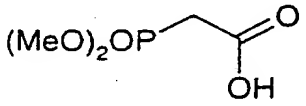
c) Compounds of the general Formula V can thereafter be converted to compounds of the general Formula VI,



(VI)

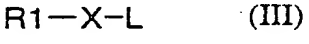
by treatment with formaldehyd in the presence of a suitable base, such as Et_2NH, under standard conditions.

However, if Y is CH(Z) then compounds of the general Formula VI can be prepared by treating compounds of the general Formula VII,



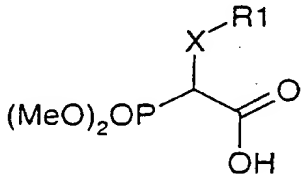
(VII)

with an alkylating agent of the general Formula III,



(III)

wherein R_1 is as defined for Formula I and L is a suitable leaving group, such as a chloro, bromo, iodo, triflate or tosyl group, in the presence of a suitable base, such as LDA or NaH, under standard conditions to give compounds of the general Formula VIII,



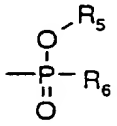
(VIII)

Compounds of the general Formula VIII can thereafter be reacted with an appropriate aldehyde CHO(Z), wherein Z is as defined for Formula I, in the presence of a suitable base, such as KOtBu, LDA or NaH, under standard conditions to give to give a compound of the general Formula VI.

d) Compounds of the general Formula VI can be further reacted with compounds of the general Formula IX

$$R_6PO_2H_2 \qquad (IX)$$

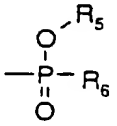
wherein R_6 is as defined for Formula I, in the presnec of a suitable reagent, such as BSA or HMDS, under standard conditions to give compounds of the general Formula I, wherein R_1, R_5, R_6 and Z are as defined above, R_2 is H, R_3 is $COOR_5$,

R_4 represents a  -group,

X is $C(Z)_2$, and Y is $C(Z)_2$.

Process B

Process B for manufacture of compounds with the general Formula I, wherein R_1, R_2, R_5, R_6, and Z are as defined above, R_3 is $COOR_5$, X is $C(Z)_2$, Y is O, and

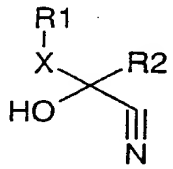
R_4 represents a  -group,

comprises the following steps:

a) Reacting a compound of the general Formula X,

R1—XCO—R2 (X)

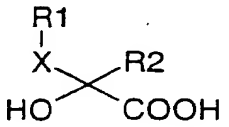
wherein R_1, R_2 and Z are as defined in Formula I and X is $C(Z)_2$ in the presence of suitable reagents, such as $TMSCN/ZnI_2$ or KCN/HOAc, under standard conditions to give compounds of the general Formula XI,



(XI)

wherein R_1 and R_2 are as defined in Formula I and X is $C(Z)_2$.

b) Compounds of the general Formula XI can thereafter be treated with suitable reagents, such as HCl or HCl/MeOH, under standard conditions to give compounds of the general Formula XII,



(XII)

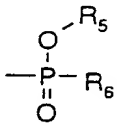
wherein R_1 and R_2 are as defined in Formula I and X is $C(Z)_2$.

c) Compounds of the general Formula XII can thereafter be reacted with compounds of the general Formula XIII,

$R_6PO_3H_2$ (XIII)

wherein R_6 is as defined in the general Formula I, which are either commercially available, well known in the literature, or are available using known techniques, in the presence of suitable coupling reagents such a DCC/DMAP, PyBop/DIPEA or $SOCl_2$, under standard

conditions to give compounds of the general Formula I, wherein R_1, R_2, R_5, R_6 and Z are as defined above, R_3 is $COOR_5$.

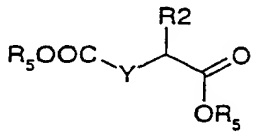
R_4 represents a  -group,

X is $C(Z)_2$ and Y is O.

Process C

Process C for manufacture of compounds with the general Formula I, wherein R_1 and R_2 are as defined above and X and Y is $C(Z)_2$ or a single bond and R_3 and R_4 are $COOR_5$, comprises the following steps,

a) reacting a compound of the general Formula XIV,

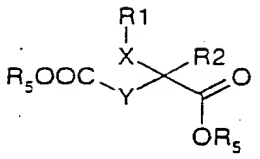


(XIV)

wherein R_2 and R_5 are as defined in Formula I and Y is $C(Z)_2$ or a single bond, which are either commercially available, well known in the literature, or are available using known techniques, with a compound of the general Formula III,

R1—X–L (III)

wherein R_1 is as defined for Formula I, X is $C(Z)_2$ and L is a suitable leaving group, such as Cl, Br, I or tosyl, in the presence of a suitable base, such as LDA or NaH under standard conditions, to give a compound of the general Formula XV,

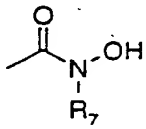


(XV)

b) hydrolysing a compound of the general Formula XV, for example by treatment with aqueous NaOH or aqueous TFA under standard conditions to give compounds of the general Formula I, wherein R_1 and R_2 are as defined above and X and Y is $C(Z)_2$ or a single bond and R_3 and R_4 are COOH.

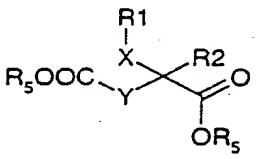
Process D

Process D for manufacture of compounds with the general Formula I, wherein R_1, R_2, R_5, R_7, X, Y and Z are as defined above, R_3 is $COOR_5$ and

R_4 represents a 

-group, comprises the following steps:

a) Compounds of the general Formula XV,

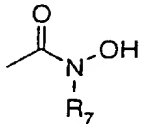


(XV)

can be reacted with compounds of the general Formula XVI,

$$HR_7NOH \qquad \text{(XVI)}$$

wherein R_7 is as defined in Formula I, in the presence of suitable reagents, such as DCC/DMAP, under standard conditions, to give compounds of the general Formula I, wherein R_1, R_2, R_5, R_7, X, Y and Z are as defined above, R_3 is $COOR_5$ and

R_4 represents a  -group.

It will be appreciated by those skilled in the art that in the process described above the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (e.g. t-butyldimethylsilyl, t-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl and benzyl. Suitable protecting groups for amino, amidino and guanidino include t-butyloxycarbonyl and benzyloxycarbonyl. Suitable protecting groups for mercapto include CO-C_{1-6} alkyl, p-methoxybenxyl and trityl. Suitable protecting groups for carboxylic acid include C_{1-6} alkyl and benzyl esters.

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

Certain protected derivatives of compounds of Formula I, which may be made prior to a final deprotection stage to form compounds of Formula I, are novel.

The use of protecting groups is described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1991). The protective group may also be a polymer resin such as Wang resin or a 2-chorotrityl chloride resin.

It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of Formula I may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds of Formula I are included within the scope of the invention.

It should also be understood that all polymorphs, amorphous forms, anhydrates, hydrates, solvates of the compounds of the present invention are within the scope of the invention.

Pharmaceutical formulations

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the present invention, or a pharmaceutically acceptable salt thereof, as active ingredient.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, intravenous, subcutaneous, tracheal, bronchial, intranasal, pulmonary, transdermal, buccal, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1–95% by weight of the preparation.

In the preparation of pharmaceutical formulations containing a compound of the present invention the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin,

or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture may then be processed into granules or pressed into tablets.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing the active ingredient and the remainder consisting, for example, of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, preservatives, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients and/or buffering ingredients. Solutions for parenteral administration may also be prepared as a dry preparation to by reconstituted with a suitable solvent before use.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 0.1 to 1000 mg per day of active substance.

Medical and pharmaceutical use

The compounds of the invention are inhibitors of carboxypeptidase U either as such or, in the case of prodrugs, after administration. The compounds of the invention are thus expected to be useful in those conditions where inhibition of carboxypeptidase U is beneficial, such as in the treatment or prophylaxis of thrombosis and hypercoagulability in blood and tissues of mammals, including man.

It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned include protein C resistance and inherited or aquired deficiences in antithrombin III, protein C, protein S and heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulatory and septic shock, circulating antiphospholipid antibodies, homocysteinami, heparin induced thrombocytopenia and defects in fibrinolysis. The compounds of the invention are thus indicated both in the therapeutic and/or prophylactic treatment of these conditions. The compounds of the invention are further indicated in the treatment of conditions where there is an undesirable excess of proCPU/CPU.

Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis) and systemic embolism usually from the atrium during arterial fibrillation or from the left ventricle after transmural myocardial infarction.

Moreover, the compounds of the invention are expected to have utility in prophylaxis of re-occlusion and restenosis (*i.e.* thrombosis) after thrombolysis, percutaneous trans-luminal

angioplasty (PTA) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general.

Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism, fibrinolytic treatment when blood is in contact with foreign surfaces in the body, such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device, and fibrinolytic treatment when blood is in contact with medical devices outside the body, such as during cardiovascular surgery using a heart-lung machine or in haemodialysis.

The compounds of the invention may also be combined and/or coadministered with any antithrombotic agent with a different mechanism of action, such as the antiplatelet agents acetylsalicylic acid ticlopidine, clopidogrel, thromboxane receptor and/or synthetase inhibitors, fibrinogen receptor antagonists, prostacyclin mimetics and phosphodiesterase inhibitors and ADP-receptor (P_2T) antagonists and thrombin inhibitors.

The compounds of the invention may further be combined and/or coadministered with thrombolytics such as tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex (APSAC), animal salivary gland plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction and stroke.

In vitro experiments

The inhibiting effect of the compounds of the present invention was estimated using the assay described in: Dirk Hendriks, Simon Scharpé and Marc van Sande, Clinical Chemistry, 31, 1936-1939 (1985); and Wei Wang, Dirk F. Hendriks, Simon S. Scharpé, The Journal of Biological Chemistry, 269, 15937-15944 (1994).

EXAMPLES

General Experimental Procedures

Mass spectra were recorded on a Finnigan MAT TSQ 700 triple quadropole mass spectrometer equipped with an electrospray interface (FAB-MS) and VG Platform II mass spectrometer equipped with an electrospray interface (LC-MS). ^{1}H NMR and ^{13}C NMR measurements were performed on Varian UNITY plus 400, 500 and 600 spectrometers, operating at ^{1}H frequencies of 400, 500 and 600 MHz respectively. Chemical shifts are given in ppm with the solvent as internal standard. Organic extracts were dried using $MgSO_4$ or Na_2SO_4 as the drying agent. Chromatography separations were performed using Merck Silica gel 60 (0.063-0.200 mm). HPLC separations were performed on a HIGHCROM KR100-10C8 column.

Example 1

5-Amino-2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxyl-pentanoic acid

(a) 5-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid

Di-*t*-butyl dicarbonate (30.8 g, 0.141 mol) was added in portions during 5 min to a solution of 5-amino-2-hydroxy-pentanoic acid (17.0 g, 0.128 mol) in 0.5 M NaOH (240 mL) and dioxan (240 mL) at 5°C. The mixture was stirred for 2.5 h at room temperature. During this time 0.5 M NaOH was added to maintain pH 9-10. The dioxan was removed under reduced pressure and the aqueous phase was washed with diethyl ether. The aqueous phase was acidified to pH 2-3 with $KHSO_4$ and extracted with ethyl acetate (3 x 300 mL). The pooled organic phases was washed with water and brine, dried and concentrated under reduced pressure to give crude 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid (22.0 g, 73.7%).

(b) 5-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester

A solution of methyl iodide (11.5 mL, 0.189 mol) in DMF (50 mL) was added dropwise during 15 min. to a mixture of 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid

(22.0 g, 94.4 mmol) and $NaHCO_3$ (11.8 g, 141 mmol) in DMF (150 mL). After stirring over night, water was added and the mixture was extracted with ethyl acetate. The pooled organic phases were washed with water and brine, dried and concentrated under reduced pressure. The crude product was purified using chromathography (heptane/ethyl acetate. 1:1) to give 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester 9.9 g, 42.5 %)

(c) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-methoxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester

A solution of PyBOP (2.1 g, 4.0 mmol) in DMF (3 mL) was added to a mixture of (1-benzyloxycarbonylamino-2-methyl-propyl)-phosphonic acid monomethyl ester (1.0 g, 3.32 mmol) and 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester (865 mg, 3.5 mmol) in DMF (4 mL) under argon. DIPEA (2.28 mL, 13.3 mmol) was added dropwise and the mixture was stirred over night. Ethyl acetate was added and the mixture was washed with 10 % $KHSO_4$, satd. $NaHCO_3$ and brine and dried. Concentration under reduced pressure followed by chromathography (heptane/EtOAc, 1:1 → 1:6) gave 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-methoxy-phosphinoyloxy]-5-*tert*-butoxy-carbonylamino-pentanoic acid methyl ester (1.21 g, 69 %).

(d) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid

1 M LiOH (5 mL) was added to a solution of 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-methoxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester (187 mg, 0.35 mmol) in acetonitrile (5 mL). The mixture was stirred at 50°C over night and concentrated under reduced pressure. The crude product was purified using chromathography (iPrOH/conc. aq. NH_3/H_2O, 4:2:1) to yield 2-[(1-benzyloxycarbonyl-amino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid (180 mg, 100 %).

(e) 5-Amino-2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-pentanoic acid

TFA (3 mL) was added to a solution of 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-*tert*-butoxycarbonylamino-pentanoic acid (150 mg, 0.3 mmol) in methylene chloride/acetonitrile (1:1, 15 mL). The solution was stirred for 120 min and concentrated under reduced pressure to give the title compound as the TFA salt (174 mg, 100 %).

^{1}H NMR (500 MHz, CD_3OD): δ 1.02 (t, 6H), 1.66-2.0 (m, 4H), 2.23 (m, 1H), 2.93 (m, 2H), 3.91 (m, 1H), 4.85 (bs, 1H), 5.12 (m, 2H), 7.28-7.42 (m, 5H).

MS (+) 403.3 (M+1).

Example 2

2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-guanidino-pentanoic acid

(a) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-5-guanidino-pentanoic acid

A solution of S-methylisothiourea hydrogen sulfate (25 mg, 90 µmol) in 1 M NaOH (0.18 mL) was added to a solution of 5-amino-2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyloxy]-pentanoic acid (36 mg, 90 µmol) and 1 M NaOH (0.18 mL) in water/MeOH (1:1, 0.4 mL). The rection mixture was stirred at 50°C for 6 h and concentrated under reduced pressure. The crude product was purified using HPLC (0-50 % acetonitrile, 0.1% TFA in water) to give the title compound as the TFA salt (19 mg, 38 %)

^{1}H NMR (500 MHz, CD_3OD): δ 1.02 (t, 6H), 1.60-1.98 (m, 4H), 2.23 (m, 1H), 3.20 (m, 2H), 3.91 (m, 1H), 4.82 (bs, 1H), 5.11 (m, 2H), 7.26-7.42 (m, 5H).

MS (+) 445 (M+1).

Example 3

5-Amino-2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-pentanoic acid

(a) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester

Thionyl chloride (49 µL, 0.67 mmol) was added dropwise to a solution of [1-(2-benzyloxy-carbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-phosphonic acid (208 mg, 0.48 mmol) in DMF (5 mL) at -20°C under argon. The mixture was stirred for 35 min at -5°C. A solution of 5-*tert*-Butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester (166 mg, 0.67 mmol) in DMF (1 mL) was added and the mixture was stirred for 90 min at room temperature. Ethyl acetate was added and the mixture was washed with 1 M HCl, dried and concentrated under reduced pressure. The crude product was purified using chromathography ($CHCl_3$/MeOH/H_2O, 10:1:0 → 10:5:1) to give 2-{[1-(2-benzyloxy-carbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid methyl ester (211 mg, 66 %).

(b) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonylamino-pentanoic acid

1 M LiOH (3.5 mL) was added to a solution of 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxy-carbonylamino-pentanoic acid methyl ester (211 mg, 0.32 mmol) in acetonitrile (3.5 mL) and the mixture was stirred for 3 h. Ethyl acetate was added and the mixture was washed with 1 M HCl, dried and concentrated to give crude 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxy-carbonylamino-pentanoic acid (208 mg, 100 %).

(c) 5-Amino-2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-pentanoic acid

TFA (5 mL) was added to a solution of 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-*tert*-butoxycarbonyl-amino-pentanoic acid (208 mg, 0.32 mmol) in acetonitrile (5 mL) and the mixture was stirred for 90 min. The reaction mixture was concentrated under reduced pressure to give the crude title compound as the TFA salt (212 mg, 100 %). 20 mg of the crude title compound was purified using chromathography (iPrOH/conc. aq. NH_3/H_2O, 4:2:1) to give the title compound as the TFA salt (19 mg, 94 %).

^{1}H NMR (500 MHz, CD_3OD): δ 0.85-0.95 (m, 6H), 1.70-2.0 (m, 4H), 2.05-2.13 (m, 1H), 2.85-3.05 (m, 2H), 3.05-3.12 (m, 1H), 4.10 (bs, 1H), 4.55 (m, 1H), 4.90 (m, 1H), 5.09 (s, 2H), 7.20-7.35 (m, 10H).

Example 4

2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-guanidino-pentanoic acid

(a) 5-Amino-2-hydroxy-pentanoic acid methyl ester

TFA (2 mL) was added to a solution of 5-*tert*-butoxycarbonylamino-2-hydroxy-pentanoic acid methyl ester in methylene chloride (10 mL) and the mixture was stirred for 3 h and then concentrated under reduced pressure to give crude 5-amino-2-hydroxy-pentanoic acid methyl ester (1 g).

(b) 5-(Guanidino-ω, ω´-bis(*tert*-Butoxycarbonyl)-2-hydroxy-pentanoic acid methyl ester

To a solution of 5-amino-2-hydroxy-pentanoic acid methyl ester (0.5 g, 2.0 mmol) in acetonitrile (5 mL) was added *tert*-butoxycarbonylimino-pyrazol-1-yl-methyl)-carbamic acid *tert*-butyl ester (0.77g, 2.5 mmol) followed by DIPEA (0.86 mL, 5 mmol). After stirring for 60 min ethyl acetate was added. The mixture was washed with 1 M HCl, satd. $NaHCO_3$ and brine, dried and concentrated under reduced pressure. The crude product was purified using chromathography (heptane/ethyl acetate, 1:0 → 1:3) to give 5-(guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)-2-hydroxy-pentanoic acid methyl ester (0.27 g, 35 %).

(c) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-Butoxycarbonyl)]-pentanoic acid methyl ester

Thionyl chloride (70 µL, 0.97 mmol) was added dropwise to a solution of [1-(2-benzyloxy-carbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-phosphonic acid (301 mg, 0.69 mmol) in DMF (5 mL) at -20°C under argon. The mixture was stirred for 20 min at

-5°C. A solution of 5-(guanidino-ω, ω´-bis(*tert*-Butoxycarbonyl)-2-hydroxy-pentanoic acid methyl ester (270 mg, 0.69 mmol) in DMF (1 mL) was added and the mixture was stirred for 180 min at room temperature. Ethyl acetate was added and the mixture was washed with 1 M HCl, dried and concentrated under reduced pressure. The crude product was purified using chromathography (toluene/ethyl acetate, 1:1 → 0:1) to give 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)]-pentanoic acid methyl ester (0.27 g, 48 %).

(d) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-Butoxycarbonyl)]-pentanoic acid

A solution of LiOH (42 mg, 1.0 mmol) in water (1.0 mL) was added to a solution of 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)]-pentanoic acid methyl ester (160 mg, 0.2 mmol) in acetonitrile (1.0 mL) and the mixture was stirred for 15 min. Ethyl acetate was added and the mixture was washed with 1 M HCl and brine, dried and concentrated to give crude 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)]-pentanoic acid (160 mg, 100 %).

(e) 2-{[1-(2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-guanidino-pentanoic acid

TFA (2 mL) was added to a solution of 2-{[1-(2-benzyloxycarbonylamino-3-phenyl-propionylamino)-2-methyl-propyl]-hydroxy-phosphinoyloxy}-5-[guanidino-ω, ω´-bis(*tert*-butoxycarbonyl)]-pentanoic acid (160 mg, 0.2 mmol) in acetonitrile (5 mL) and the mixture was stirred for 60 min and then concentrated under reduced pressure. The crude product was purified using chromathography (iPrOH/conc. aq. NH_3/H_2O, 4:2:1) to give the title compound as the TFA salt (30 mg, 21 %).

^{1}H NMR (500 MHz, CD_3OD): δ 0.80-0.98 (m, 6H), 1.53-1.95 (m, 4H), 2.01-2.30 (m, 1H), 2.90 (m, 1H), 3.10-3.30 (m, 3H), 3.94-4.10 (m, 1H), 4.41-4.55 (m, 1H), 4.68 (m, 1H), 5.03 (m, 2H), 7.18-7.37 (m, 5H).

MS (+) 592 (M+1).

Example 5

2-Hydroxycarbamoyl-4-piperidin-4-yl-butyric acid

(a) Piperidin-4-yl-acetic acid

Pyridin-4-yl-acetic acid hydrochloride (20.0 g, 115 mmol) was added to water/25 % ammonia (125 mL:10mL). The mixture was degassed and flushed with nitrogen before addition of rhodium on activated alumina (0.45 g). The mixture was again degassed, then stirred in a hydrogen atmosphere at 50 bar for 16 h. Filtration of the reaction mixture through filter paper afforded the bulk of the catalyst which was recycled after washing with methanol. The filtrate was then filtered through Celite and concentrated to afford a white solid (19.7 g, 96 % yield).

(b) 4-Carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of piperidin-4-yl-acetic acid (19.7 g, 148 mmol) in THF-water (417 mL, 1:1) was added di-tert-butyl dicarbonate (32.3 g, 148 mmol) and sodium bicarbonate (12.5 g, 148 mmol), and the reaction stirred at room temperature for 16 h. THF was then removed under reduced pressure and the aqueous phase extracted with dichloromethane and the organic layer discarded. The aqueous layer was then acidified to pH 1-2 with 1 M HCl solution and extracted with ethyl acetate. The organic phase wase washed with brine, dried and concentrated under reduced pressure to give 4-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (16.7 g, 46 %).

(c) 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of 4-carboxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (16.7 g, 69.0 mmol) in THF (100 mL) was added diborane (151 mL, 1.0 M solution in THF) over a period of 10 min at 0°C. Hydrogen gas was rapidly evolved and after gas evolution had ceased the reaction was stirred at room temperature for 1 h. The reaction mixture was again cooled to 0°C, and 1 M aqueous HCl was added dropwise to the reaction mixture with further evolution of hydrogen. Addition of HCl was continued until the evolution of hydrogen had almost ceased. The mixture was then stirred for 10 min and made basic (pH

13-14) by the addition of 1 M NaOH solution. The aqueous solution was extracted with ethyl acetate, the organic phase washed with brine, dried and concentrated under reduced pressure to yield 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (15.2 g, 97 %).

(d) 4-(2-Oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester

Periodinane (36.1 g, 85.2 mmol) was added to 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (15.0 g, 65.5 mmol) in CH_2Cl_2 (230 mL) and stirred for 90 min. Diethyl ether (560 ml) was added and precipitates were removed by extraction with 10 % $Na_2S_2O_3$/saturated $NaHCO_3$ (1:1, 350 mL). The organic layer was washed with 0.5 M NaOH solution and brine. The organic phase was dried and concentrated under reduced pressure to yield 4-(2-Oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (8.50 g, 57 %).

(e) 4-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester.

To a solution of meldrums acid (1.68 g, 11.66 mmol) and 4-(2-oxo-ethyl)-piperidine-1-carboxylic acid *tert*-butyl ester (2.21 g, 9.72 mmol) in dichloromethane (40 mL) was added acetic acid (0.055 mL, 0.972 mmol) and piperidine (0.096 mL, 0.972 mmol). The mixture was heated at reflux for 3 h, and then allowed to attain room temperature. After being diluted with *tert*-butyl methyl ether, the mixture was washed with $NaHCO_3$ (sat.) and brine. The organic phase was dried, filtered and concentrated. The residue was dissolved in a mixture of EtOH (40 mL) and acetic acid (20 mL). The solution was cooled to 0°C, and $NaBH_4$ (0.554 g, 14.6 mmol) was added in portions after which the solution was allowed to stir for 30 min at rt and then acidified to pH 3 with 1 M HCl. The solution was extracted several times with dichloromethane. The combined organic phases were dried, filtered, concentrated and filtered through a pad of silica gel (dichloromethane). The solvent was evaporated to give 4-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester as a colorless oil (2.30 g, 65 %) which solidified on standing.

(f) 2-Hydroxycarbamoyl-4-piperidin-4-yl-butyric acid.

A GC-autosample vial (2 mL) equipped with a septum cap and a small stirbar was charged with 4-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester (17.8 mg, 0.05 mmol) and flushed with nitrogen. N,O-Bis(trimethylsilyl)-hydroxylamine (0.2 mL) was added via syringe and the resulting solution was stirred at rt over night. The mixture was concentrated under vacuum and the residue dissolved in dichloromethane/MeOH (4:1) and applied onto a small plug of ion exchange resin (200 mg, isolute™, aminoresin), washed with dichloromethane/MeOH (4:1) and then eluted with dichloromethane/MeOH/AcOH (3:1:1). The eluate was concentrated, the residue dissolved in dichloromethane/TFA (1:1, 2 mL) and stirred for 1h at room temperature. Evaporation of the solvent gave the title compound as the TFA salt (16 mg, 93 %) as a colourless oil.

^{1}H NMR (600 MHz, CD_3OD) δ 1.21-1.40 (m, 4H), 1.53-1.62 (m, 1H), 1.80-1.99 (m, 4H), 2.90-2.98 (m, 2H), 3.06 (t, 1H), 3.32-3.39 (m, 2H).

M (+) 231 (M+1).

Example 6

N-hydroxy-2-piperidin-3-ylmethyl-malonamic acid

(a) 3-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester

3-Hydroxymethyl-piperidine (20.0 g, 0.17 mmol) in acetonitrile was treated with di-tert-butyl dicarbonate (37.9 g, 0.17 mol) and DMAP (2.13 g, 1.74 mmol). The reaction mixture was stirred at ambient temperature for 5 h and then concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc, 70:30) to give 3-hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (16.0 g, 44 %).

(b) 3-Formyl-piperidine-1-carboxylic acid tert-butyl ester

Periodinane (18.2 g, 42.9 mmol) was added to 3-hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (7.10 g, 33.0 mmol) in CH_2Cl_2 (230 mL) and stirred for 90 min. Diethyl ether (230 mL) was added and precipitates were removed by extraction with 10 % $Na_2S_2O_3$/saturated $NaHCO_3$ (1:1, 230 mL). The organic layer was washed with 0.5 M NaOH solution and brine. The organic phase was dried and concentrated under reduced pressure to yield 3-Formyl-piperidine-1-carboxylic acid tert-butyl ester (6.50 g, 93 %).

(c) N-Hydroxy-2-piperidin-3-ylmethyl-malonamic acid

The title compound was prepared from 3-formyl-piperidine-1-carboxylic acid tert-butyl ester by the method described in Example 5. Yield: (50 %).

^{1}H NMR (600 MHz, CD_3OD) δ 1.18-1.30 (m, 1H), 1.61-1.99 (m, 6H), 2.64 (t, 1H), 2.86 (t, 1H), 3.20-3.38 (m, 3H).

M (+) 217 (M+1).

Example 7

2-(6-Amino-pyridin-3-ylmethyl)-*N*-hydroxy-malonamic acid.

The title compound was prepared from (5-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester by the method described in Example 5. Yield: (23 %).

^{1}H NMR (600 MHz, CD_3OD) d 2.99-3.10 (m, 2H), 3.36-4.01 (m, 1H), 6.94 (d, 1H), 7.64 (s, 1H), 7.82 (d, 1H).

M (+) 226 (M+1).

Example 8

2-(2-Amino-pyridin-4-ylmethyl)-*N*-hydroxy-malonamic acid.

(a) (4-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester

(4-Hydroxymethyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester (1.91 g, 8.51 mmol) was dissolved in dry DMSO (10 mL) and the reaction flask immersed in a waterbath at 15°C. Triethylamine (1.72 g, 17.0 mmol) was added followed by sulfur trioxide pyridine complex (2.41 g, 15.1 mmol). The reaction mixture was stirred for 2 h and poured onto crushed ice and the product extracted with $CHCl_3$. The organic extract was washed with water, dried concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc, 80:20) to give (4-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester (1.57 g, 83 %).

(b) 2-(2-Amino-pyridin-4-ylmethyl)-*N*-hydroxy-malonamic acid

The title compound was prepared from (4-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester by the method described in Example 5. Yield: (48 %).

^{1}H NMR (600 MHz, CD_3OD) δ 3.10 (dd, 1H), 3.19 (dd, 1H), 3.47 (dd, 1H), 6.77 (d, 1H), 7.82 (s, 1H), 7.71 (d, 1H).
M (+) 226 (M+1).

Example 9

2-[2-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-ethyl]-malonic acid.

To a solution of 4-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-ethyl]-piperidine-1-carboxylic acid *tert*-butyl ester (17.8 mg, 0.05 mmol) in acetic acid (1 mL) was added 6 M HCl (2 mL). The solution was stirred at room temperature over night and then concentrated to yield the title compound as the hydrochloric acid salt (15 mg, 100 %).
^{1}H NMR (600 MHz, CD_3OD) δ 1.30-1.40 (m, 4H), 1.57-1.64 (m, 1H), 1.83-1.90 (m, 1H), 1.90-1.98 (m, 1H), 3.31-3.39 (m, 2H).
M (+) 216 (M+1).

Example 10

2-[2-(1-*tert*-Butoxycarbonyl-piperidin-3-yl)-methyl]-malonic acid.

The title compound was prepared from 3-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-piperidine-1-carboxylic acid *tert*-butyl ester by the method described in Example 9. Yield: (100 %).
^{1}H NMR (600 MHz, CD_3OD) δ 1.20-1.30 (m, 1H), 1.63-1.76 (m, 1H), 1.78-1.97 (m, 5H), 2.65 (t, 1H), 2.83-2.92 (m, 1H), 3.29-3.38 (m, 2H), 3.42-3.48 (m, 1H).
M (+) 202 (M+1).

Example 11

2-[2-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-methyl]-malonic acid

(a) Piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester

Piperidine-4-carboxylic acid (24.5 g, 0.19 mmol) in THF/water (1:1, 417 mL) was treated with di-tert-butyl dicarbonate (41.49 g, 0.19 mol) and sodium bicarbonate (16.0 g, 0.19 mol). The reaction mixture was stirred at ambient temperature for 16 h. The THF was then removed under reduced pressure and the aqueous phase washed with dichloromethane. The aqueous layer was then acidified to pH 1-2 with 1 M HCl solution and extracted with ethyl

acetate. The organic phase was washed with brine and dried to give piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester (35.9 g, 83 %).

(b) 4-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of piperidine-1,4-dicarboxylic acid mono-*tert*-butyl ester (19.3 g, 84.0 mmol) in THF (100 mL) was added diborane (185 mL, 1.0 M solution in THF) over a period of 10 min at 0°C. Hydrogen gas was rapidly evolved and after gas evolution had ceased the reaction was stirred at room temperature for 1 h. The reaction mixture was again cooled to 0°C, and 1 M aqueous HCl was added dropwise to the reaction mixture with further evolution of hydrogen. Addition of HCl was continued until the evolution of hydrogen had almost ceased. The mixture was then stirred for 10 min and made basic (pH 13-14) by the addition of 1 M NaOH solution. The aqueous solution was extracted with ethyl acetate, the organic phase washed with brine, dried and concentrated under reduced pressure to yield 4-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (18.12 g, 100 %).

(c) 4-Formyl-piperidine-1-carboxylic acid *tert*-butyl ester

Periodinane (26.9 g, 63.5 mmol) was added to 4-Hydroxymethyl-piperidine-1-carboxylic acid *tert*-butyl ester (10.5 g, 48.8 mmol) in CH_2Cl_2 (200 mL) and stirred for 90 min. Diethyl ether (560 mL) was added and precipitates were removed by extraction with 10 % $Na_2S_2O_3$/saturated $NaHCO_3$ (1:1, 300 mL). The organic layer was washed with 0.5 M NaOH solution and brine. The organic phase was dried and concentrated under reduced pressure. Purification using flash chromatography (hexane/EtOAc, 8:2) gave 4-Formyl-piperidine-1-carboxylic acid *tert*-butyl ester (8.5 g, 81 %).

(d) 2-[2-(1-*tert*-Butoxycarbonyl-piperidin-4-yl)-methyl]-malonic acid.

The title compound was prepared from 4-Formyl-piperidine-1-carboxylic acid *tert*-butyl ester by the method described in Example 5 and 9. Yield: (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 1.38-1.48 (m, 2H), 1.61-1.75 (m, 1H), 1.82-1.90 (m, 2H), 1.92-2.02 (m, 2H), 2.90-3.01 (m, 2H), 3.35-3.42 (m, 2H), 3.42-3.48 (m, 1H).

M (+) 202 (M+1).

Example 12

2-(6-*tert*-Butoxycarbonylamino-pyridin-3-ylmethyl)-malonic acid.

The title compound was prepared from [5-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-pyridin-2-yl]-carbamic acid *tert*-butyl ester by the method described in Example 9. Yield: (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 3.08 (d, 2H), 3.66 (t, 1H), 6.98 (d, 1H), 7.73 (s, 1H), 7.92 (d, 1H).

M (+) 211 (M+1).

Example 13

2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethyl)-malonic acid.

The title compound was prepared from [4-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-ylmethyl)-pyridin-2-yl]-carbamic acid *tert*-butyl ester by the method described in Example 9. Yield: (100 %).

^{1}H NMR (600 MHz, CD_3OD) δ 3.10 (d, 2H), 3.79 (t, 1H), 6.84 (d, 1H), 7.92 (s, 1H), 7.77 (d, 1H).

M (+) 211 (M+1).

Example 14

2-(2-Amino-pyridin-4-ylmethyl)-succinic acid

(a) 2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester

Butyllithium (1.6 M in hexane, 14.8 ml, 23.7 mmol) was added dropwise to a solution of 2-(diethoxy-phosphoryl)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (9.50 g, 23.7 mmol in THF (75 mL) at 0°C under nitrogen. After stirring at 0°C for 1 h, the solution was transferred to a solution of (4-Formyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester (3. 70 g, 16.6 mmol) in THF (75 mL). The resulting reaction mixture was stirred at 0°C for 1 h before being allowed to warm to 25 °C, and the mixture was stirred overnight. Water (400 mL) was added and the product extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried and concentrated. Flash chromatography (hexane/EtOAc, 4:1) gave 2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester 4.30 g (55 %).

(b) 2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethyl)-succinic acid 1-*tert*-butyl ester

2-(2-*tert*-Butoxycarbonylamino-pyridin-4-ylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (2.81 g, 7.60 mmol) and Pd/C (10 %, 400 mg) were suspended in EtOH and hydrogenated at 41 atm. and 28°C for 3 days. The catalyst was removed from the reaction mixture by filtration. The catalyst was washed with EtOH (96 %). 1 M K_2CO_3 (30 mL) was added to the filtrate followed by addition of water (50 mL). After 2 days the reaction mixture was evaporated to ca 80 mL, then brine (10 mL) was added and the reaction mixture extracted with ether. The aqueous phase was acidified to pH=3 and extracted with chloroform. Methanol (25 mL) was added and the reaction mixture was dried (Na_2SO_4 + $CaSO_4$) and filtered to give 2-(2-*tert*-butoxycarbonylamino-pyridin-4-ylmethyl)-succinic acid 1-*tert*-butyl ester (1.90 g, 83 %).

(c) 2-(2-Amino-pyridin-4-ylmethyl)-succinic acid

To a solution of 2-(2-*tert*-butoxycarbonylamino-pyridin-4-ylmethyl)-succinic acid 1-*tert*-butyl ester (164 mg, 0.43 mmol) in methylene chloride (1.5 mL) was added TFA (1.5 mL). The reaction mixture was stirred for 2.5 h and then concentrated under reduced pressure. The residue was lyophilized to give the title compound as the TFA salt (126mg, 87 %)

^{1}H NMR (500 MHz, D_2O): δ 2.58-2.80 (m, 2H), 2.88-3.07 (m, 2H), 3.13-3.26 (m, 1H), 6.79-6.84 (dd, 1H), 6.84-6.88 (s, 1H), 7.69-7.75 (d, 1H).

MS (+) 225 (M+1).

Example 15

trans-2-(4-Amino-cyclohexylmethyl)-succinic acid

(a) 4-[*N*-(*tert*-Butoxycarbonyl)amino]-cyclohexane carboxylic acid

To a solution of *cis*-4-aminocyclohexane carboxylic acid (9.90 g, 69.0 mmol) in water (120 mL) and dioxane (120 mL) was added KOH (3.73 g, 56 mmol) followed by di-*tert*-butyl dicarbonate (15.3 g, 70.0 mmol). The reaction mixture was stirred at room temperature overnight. Water was added and the product was extracted with $CHCl_3$. The combined organic extracts were washed with water, dried and concentrated under reduced pressure to give 4-[*N*-(*tert*-butoxycarbonyl)amino]-cyclohexane carboxylic acid (14.1 g, 84 %).

(b) [4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid *tert*-butyl ester

A solution of 4-[*N*-(*tert*-butoxycarbonyl)amino]-cyclohexane carboxylic acid (11.95 g, 49.0 mmol), *O,N*-dimethylhydroxylamine (4.88 g, 50.0 mmol), DCC (9.60 g, 50 mmol) and triethylamine (5.06 g, 50.0 mmol) in DMF (150 mL) was stirred at room temperature overnight. Water (500 mL) was added and the mixture was extracted with $CHCl_3$. The organic phase was washed with water, dried and concentrated under reduced pressure. Purification by flash chromatography (hexane/EtOAc 1:1) gave [4-(methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (8.50 g, 61 %).

(c) (4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester

[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (7.50 g, 26.2 mmol) in dry ether (150 ml) was reduced with an excess $LiAlH_4$. The reaction mixture was quenched by careful addition of water and extracted with $CHCl_3$. The mixture was dried and concentrated under reduced pressure to give (4-formyl-cyclohexyl)-carbamic acid *tert*-butyl ester (6.30 g, 93 %).

(d) trans-[4-(Benzylimino-methyl)-cyclohexyl]-carbamic acid tert-butyl ester

A mixture of (4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester (3.80 g, 16.7 mmol), benzylamine (1.82 g, 16.7 mmol), acetic acid (0.01 g, 16.7 mmol) and anhydrous magnesium sulfate (4.01 g, 33.3 mmol) in methylene chloride (20 mL) was stirred for 5 days. The mixture was filtered through Celite and concentrated under reduced pressure to give trans-[4-(benzylimino-methyl)-cyclohexyl]-carbamic acid tert-butyl ester (5.10 g, 97 %) as a 97:3 *trans:cis* mixture.

(e) trans-(4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester

A solution of trans-[4-(benzylimino-methyl)-cyclohexyl]-carbamic acid tert-butyl ester (2.50 g, 8.00 mmol) and oxalic acid (0.80 g) in water/THF (50 mL, 1:1) was stirred for 10 h at room temperature. The reaction mixture was concentrated under reduced pressure and methylene chloride (50 mL) was added to the residue. The organic phase was dried and concentrated under reduced pressure to give trans-(4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester (1.3 g, 80 %).

(f) trans 2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester

Butyllithium (1.6 M in hexane, 5.0 ml, 8.00 mmol) was added dropwise to a solution of 2-(diethoxy-phosphoryl)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (3.21 g, 8.00 mmol) in THF (25 mL) at 0°C under nitrogen. After stirring at 0°C for 1 h, the solution was transferred to a solution of trans-(4-Formyl-cyclohexyl)-carbamic acid *tert*-butyl ester (1.30 g, 5.72 mmol) in THF (10 mL). The resulting mixture was stirred at 0°C for 1 h and at room temperature overnight. Water was added and the product extracted with CH_2Cl_2. The organic phase was dried and concentrated under reduced pressure. Flash chromatography (hexane/EtOAc, 80:20) gave trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (1.10 g)

(g) trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethyl)-succinic acid 1-*tert*-butyl ester

A solution of trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethylene)-succinic acid 4-benzyl ester 1-*tert*-butyl ester (243 mg, 0.51 mmol) and palladium (5 % on charcoal) in ethanol (15 mL) was hydrogenated at 4 bar for 3 h. The catalyst was removed from the reaction mixture by filtration. The catalyst was washed with ethanol and the solution was concentrated under reduced pressure to give crude trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethyl)-succinic acid 1-*tert*-butyl ester (217 mg, >100 %).

(h) trans-2-(4-Amino-cyclohexylmethyl)-succinic acid

To a solution of trans-2-(4-*tert*-Butoxycarbonylamino-cyclohexylmethyl)-succinic acid 1-*tert*-butyl ester (200 mg, 0.52 mmol) in methylene chloride (1.32 g, 15.6 mmol) was added triethylsilane (150 mg, 1.30 mmol) followed by TFA (770 mg, 6.75 mmol). The reaction mixture was stirred for 2.5 h and then concentrated under reduced pressure. Purification by HPLC (0-80 % acetonitrile, 0.1 % TFA in water) gave the title compound as the TFA salt (60 mg, 34 %)

^{1}H NMR (500 MHz, D_2O): δ 0.99-1.11 (m, 2H), 1.30-1.46 (m, 4H), 1.54-1.62 (m, 1H), 1.79-1.86 (m, 1H), 1.89-1.96 (m, 1H), 1.99-2.06 (m, 2H), 2.58-2.71 (m, 2H), 2.85-2.95 (m, 1H), 3.08-3.17 (m, 1H).

MS (+) 230 (M+1).

Example 16

2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-hydroxy-succinamic acid

(a)*N*-Benzyl-*N*-benzyloxy-2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-succinamic acid *tert*-butyl ester

To a solution of 2-(2-*tert*-butoxycarbonylamino-pyridin-4-ylmethyl)-succinic acid 1-*tert*-butyl ester (0.67 g, 1.76 mmol) in CH_2Cl_2 (25 mL) was added *N*-benzyl-*N*-benzyloxy amine (0.42 g, 1.94 mmol), DCC (0.40 g, 1.94 mmol) and DMAP (0.02 g, 0.17 mmol) and the mixture was stirred overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried and filtered and the residue purified by flash chromatography (hexane/EtOAc, 4:1) to give *N*-Benzyl-*N*-benzyloxy-2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-succinamic acid *tert*-butyl ester (0.51 g, 50 %).

(b) 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-benzyloxy-succinamic acid

To a solution of *N*-Benzyl-*N*-benzyloxy-2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-succinamic acid *tert*-butyl ester (1.0 g, 1.7 mmol) in methylene chloride (10 mL) was added TFA (4 mL) at 0°C. The reaction mixture was stirred for 4 hs and then concentrated under reduced pressure to give crude 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-benzyloxy-succinamic acid as the TFA salt (0.9 g, 100 %).

(c) 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-hydroxy-succinamic acid

A solution of 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-benzyloxy-succinamic acid (0.9 g, 1.7 mmol) and palladium (0.5g, 5 % on charcoal) in methanol (100 mL) was hydrogenated at 1 bar for 2 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($CHCl_3$/MeOH/H_2O, 10:5:1) to give the title compound (123 mg, 22 %).

^{1}H NMR (600 MHz, CD_3OD): δ 2.50-3.03 (m, 5H), 4.72 (q, 2H), 6.65 (d, 1H), 7.18-7.31 (m, 6H), 7.53 (d, 1H), 7.65 (s, 1H).

MS (+) 330 (M+1).

Example 17

2-(6-amino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid

(a) 2-(6-*tert*-Butoxycarbonylamino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid ethyl ester

A solution of (3-Phenyl-propyl)-phosphinic acid (0.579g 3.143mmol) and 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-acrylic acid ethyl ester (0.327g 1.067 mmol) in MeCN (7.5 mL) was degassed using the freeze-thaw technique. BSA (2.55g 12.57 mmol) was added and the mixture was stirred for 3 days and concentrated under reduced pressure. The residue was dissolved in chloroform, washed with $NaHCO_3$ and brine, dried and concentrated under reduced pressure. Flash chromatography (CH_2Cl_2/MeOH, 8:2) gave 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid ethyl ester (0.240g, 16%).

(b) 2-(6-*tert*-Butoxycarbonylamino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid

To a solution of 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid ethyl ester (0.240g 0.489 mmol) in MeCN (3 mL) was added a solution of LiOH (0.059 g 2.45 mmol) in H_2O (3 mL). The mixture was then stirred at 20°C for 1.5 hours. Ethylacetate was added and the mixture was washed with 1 M HCL and brine and filtered to give 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid (0.174 g, 77%) as white crystals.

(c) 2-(6-Amino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid

To a mixture of 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid (0.170 g. 0.367 mmol) in ethylacetate (3 mL) at 4°C was slowly added ethylacetat (4 mL. saturated with HCl(g)). The mixture was then stirred for 22 h. Concentration under reduced pressure gave the title compound (0.124 g, 93%) as the hydrochloride salt.

^{1}H NMR (300 MHz, CD_3SOCD_3): δ 1.52-1.72 (m, 4H), 1.88-1.96 (m, 2H), 2.47-2.49 (t,1H), 2.57-2.62 (m, 2H), 2.77-2.82 (m, 2H), 6.94-6.97 (d,1H), 7.15-7.29 (m, 4H), 7.75-7.80 (m, 2H), 8.05 (s, 1H)
MS (+) 363 (M+1).

Example 18
2-(6-Amino-5-methyl-pyridin-3-ylmethyl)-3-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyl]-propionic acid

(a) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoylmethyl]-3-(6-bis(tert-butoxycarbonyl)amino-5-methyl-pyridin-3-yl)-propionic acid ethyl ester
A solution of 2-(6-bis(tert-butoxycarbonyl)amino-5-methyl-pyridin-3-ylmethyl)-acrylic acid ethyl ester (0.6 g, 1.43 mmol) and (1-benzyloxycarbonylamino-2-methyl-propyl)-phosphinic acid (0.678 g, 2.5 mmol) in dry acetonitrile (10 mL) was degassed using the freeze-thaw technique. Bistrimethylsilylacetamide (5 mL, 20.3 mmol) was added under argon. The resulting mixture was stirred at room temperature for 84 h and then concentrated under reduced pressure. The remaining mixture was dissolved in chloroform and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with chloroform and EtOAc. The combined organic extracts were dried and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/EtOH, 100:20 → 100:25) to yield 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoylmethyl]-3-(6-bis(tert-butoxycarbonyl)amino-5-methyl-pyridin-3-yl)-propionic acid ethyl ester (650 mg, 65,9%)

(b) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoylmethyl]-3-(6-tert-butoxycarbonylamino-5-methyl-pyridin-3-yl)-propionic acid
1 M LiOH (2 mL) was added dropwise to a solution of 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoylmethyl]-3-(6-bis(tert-butoxycarbonyl)amino-5-methyl-pyridin-3-yl)-propionic acid ethyl ester (100 mg, 0.145 mmol) in acetonitrile (2 mL). The mixture was stirred overnight and concentrated under reduced pressure. The mixture was purified by column chromatography (isopropanol/concentrated aqueous NH_3/water, 4:2:1) to give unpure product. The unpure product was stirred with MeOH,

filtered and concentrated under reduced pressure. The crude product was stirred with EtOH, filtered and concentrated under reduced pressure. The crude product was stirred with ethylacetate/ethanol, filtered and concentrated under reduced pressure to give 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoylmethyl]-3-(6-tert-butoxycarbonylamino-5-methyl-pyridin-3-yl)-propionic acid (52 mg, 63.8 %).

(c) 2-(6-Amino-5-methyl-pyridin-3-ylmethyl)-3-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoyl]-propionic acid

A solution of 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoylmethyl]-3-(6-tert-butoxycarbonylamino-5-methyl-pyridin-3-yl)-propionic acid (52 mg, 0.09 mmol) and ethylacetate (6 mL, saturated with HCl (g)) was stirred for 20 min. The mixture was concentrated under reduced pressure, washed with acetonitrile and dissolved in ethanol and petroleumether. The solution was concentrated under reduced pressure to give the title compound (41 mg, 91.3 %) as the hydrochloride salt.

^{1}H NMR (600 MHz, D_2O): δ 0.99-1.05 (m,6H), 1.75-1.85 (m, 1H), 2.10-2.28 (m, 5H) 2.68-3.15 (m, 3H), 3.75-3.81 (m, 1H), 5.04-5.19 (m, 2H), 7.20-7.37 (m, 5H), 7.51-7.71 (m, 2H).

MS (+) 501 (M+1)

Example 19

2-(6-Amino-pyridin-3-ylmethyl)-3-methyl-succinic acid

(a) 2-Ethoxycarbonyl-3-methyl-succinic acid diethyl ester

A solution of diethylmalonate (2.44g, 15 mmol) and cesium fluoride (2.32g, 15mmol) in DMF (20 mL) was stirred for 1 h at room temperature under argon. A solution of 2-methanesulfonyloxy-propionic acid ethyl ester (1.0 g, 5 mmol) in DMF (5 mL) was added and the mixture was stirred at 45°C overnight. The mixturewas poured into H_2O and extracted with ethyl acetate. The organic layers were washed with water, dried, and concentrated under reduced pressure. The crude product was purified by vacuum distillation. The product was purified by column chromatography (petroleumether/ethyl acetate, 4:1) to give 2-(6-amino-pyridin-3-ylmethyl)-3-methyl-succinic acid (0.5g, 37.7%).

(b) 2-(6-tert-Butoxycarbonylamino-pyridin-3-ylmethyl)-2-ethoxycarbonyl-3-methyl-succinic acid diethyl ester

A solution of 2-(6-amino-pyridin-3-ylmethyl)-3-methyl-succinic acid (300mg, 1.15 mmol) and NaH (30 mg, 1.25 mmol) in DMF (1 mL) was stirred at room temperature for 1 h under argon. A solution of (5-bromomethyl-pyridin-2-yl)-carbamic acid tert-butyl ester (330 mg, 1.15 mmol) in DMF (1 mL) was added and the reaction mixture was stirred for 24 h. The reaction was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated under reduced pressure. The product was purified by column chromatography (petroleumether/ethyl acetate, 4:1) to give 2-(6-tert-butoxycarbonylamino-pyridin-3-ylmethyl)-2-ethoxycarbonyl-3-methyl-succinic acid diethyl ester (220 mg, 40.9%).

(c) 2-(6-Amino-pyridin-3-ylmethyl)-3-methyl-succinic acid

A solution of 2-(6-tert-butoxycarbonylamino-pyridin-3-ylmethyl)-2-ethoxycarbonyl-3-methyl-succinic acid diethyl ester (94 mg, 0.20 mmol) in concentrated aqueous HCl (4 mL) was stirred at reflux overnight. The mixture was concentrated under reduced pressure and freeze dried to give the title compound as the HCl salt (50mg, 90.3%)

^{1}H NMR (400 MHz, D_2O): δ 1.22-1.35 (m, 3H), 2.77-3.08 (m, 4H), 6.99-7.05 (d, 1H), 7.70 (s, 1H), 7.84-7.91 (m, 1H).

MS (+) 239 (M+1)

Example 20

2-(6-Amino-pyridin-3-ylmethyl)-3-phenethyl-succinic acid

(a) 2-Ethoxycarbonyl-3-phenethyl-succinic acid diethyl ester

A solution of diethylmalonate (240.2 mg, 1.5 mmol) and NaH (43.2 mg, 1.8 mmol) in THF (3 ml) was stirred for one hour at room temperature under argon. 2-(4-Nitro-benzenesulfonyloxy)-4-phenyl-butyric acid ethyl ester (590 mg, 1.5 mmol) and DMPU (192.2 mg, 1.5 mmol) was added and the mixture was stirred at room temperature for three days. The reaction was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with water and concentrated under reduced pressure. The product was purified

by column chromatography (petroleumether/ethyl acetate, 4:1) to give 2-ethoxycarbonyl-3-phenethyl-succinic acid diethyl ester (274 mg, 52.1%).

(b) 2-(6-tert-Butoxycarbonylamino-pyridin-3-ylmethyl)-2-ethoxycarbonyl-3-phenethyl-succinic acid diethyl ester

A solution of 2-(6-amino-pyridin-3-ylmethyl)-3-phenethyl-succinic acid (9.3 mg, 0.027 mmol) and NaH (1.39 mg, 0.032 mmol) in DMF (0.5 ml) was stirred for 15 minutes at room temperature. (5-Bromomethyl-pyridin-2-yl)-carbamic acid tert-butyl ester (8.76 mg, 0.031 mmol) was added and the mixture was stirred at room temperature over night. The reaction was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with water and concentrated under reduced pressure. The product was purified by column chromatography (heptane/ethyl acetate, 2:1) to give 2-(6-tert-butoxycarbonyl-amino-pyridin-3-ylmethyl)-2-ethoxycarbonyl-3-phenethyl-succinic acid diethyl ester (3.8 mg, 25.7 %).

(c) 2-(6-Amino-pyridin-3-ylmethyl)-3-phenethyl-succinic acid

A solution of 2-(6-tert-butoxycarbonylamino-pyridin-3-ylmethyl)-2-ethoxycarbonyl-3-phenethyl-succinic acid diethyl ester (94 mg, 0.169 mmol) in concentrated HCl (7 ml) was stirred at reflux for 24 hours. The mixture was concentrated under reduced pressure and freeze dried to give the title compound as the HCl salt (55 mg, 99.2 %).

^{1}H NMR (400 MHz, D_2O): δ 1.63-1.98 (m, 2H), 2.42-2.85 (m, 4H), 3.00-3.60(m, 2H), 6.85-6.98 (m, 1H), 7.10-7.29 (m, 5H), 7.76-8.05 (m, 2H).

MS (+) 329 (M+1)

Example 21

2-(6-Amino-pyridin-3-ylmethyl)-3-butyl-succinic acid

(a) 2-Butyl-3-ethoxycarbonyl-succinic acid diethyl ester

A solution of diethylmalonate (3.589 g, 0.022 mol) and cesium fluoride (3.406 g, 0.024 mol) in DMF (50 ml) was stirred for one hour at room temperature under argon. 2-Bromo-hexanoic acid ethyl ester (5 g, 0.022 mol) was added and the mixture was stirred at 100 °C and then at 65°C over night. The reaction was poured into H_2O and extracted with ethyl

acetate. The organic layer was washed with water and concentrated under reduced pressure. The product was purified by column chromatography (heptane/ethyl acetate, 1:2) to give 2-butyl-3-ethoxycarbonyl-succinic acid diethyl ester (5.0 g, 73.8 %).

(b) 2-(6-tert-Butoxycarbonylamino-pyridin-3-ylmethyl)-3-butyl-2-ethoxycarbonyl-succinic acid diethyl ester

A solution of 2-butyl-3-ethoxycarbonyl-succinic acid diethyl ester (1 g, 3 mmol) and NaH (119 mg, 5 mmol) in DMF (20 ml) was stirred for 60 minutes at 0°C under argon. (5-Bromomethyl-pyridin-2-yl)-carbamic acid tert-butyl ester (1.425 g, 5 mmol) was added and the mixture was stirred at room temperature for one week. Ethanol (1 ml) was added and the reaction was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with water and concentrated under reduced pressure. The product was purified by column chromatography (heptane/ethyl acetate, 4:1 to 1:1) to give 2-(6-tert-butoxycarbonylamino-pyridin-3-ylmethyl)-3-butyl-2-ethoxycarbonyl-succinic acid diethyl ester (1.2 g, 71.3 %).

(c) 2-(6-Amino-pyridin-3-ylmethyl)-3-butyl-succinic acid

A solution of 2-(6-tert-butoxycarbonylamino-pyridin-3-ylmethyl)-3-butyl-2-ethoxycarbonyl-succinic acid diethyl ester (50 mg, 0.098 mmol) in concentrated HCl (4 ml) was stirred at reflux for 24 hours. The mixture was concentrated under reduced pressure and freeze dried to give the title compound as the HCl salt (28 mg, 89.9 %).
^{1}H NMR (400 MHz, D_2O): δ 0.83-0.91 (m, 3H), 1.18-1.40 (m, 4H), 1.50-1.82 (m, 2H), 2.67-2.75 (m, 12H), 2.78-2.85 (m, 2H), 2.89-3.03 (m, 1H), 6.97-7.09 (m, 1H), 7.63-7.67 (m, 1H), 7.80-7.85 (m, 1H).
MS (+) 281 (M+1)

Abbreviations

Ac = acetate

aq = aqueous

AIBN = α,α´-azoisobutyronitrile

Bn = benzyl

BSA = N,O-bis(trimethylsilyl)acetamide

Bu = butyl

Bz = benzoyl

DCC = dicyclohexylcarbodiimide

DIAD = diisopropyl azodicarboxylate

DIPEA = diisopropylethylamine

DMAP = N,N-dimethyl amino pyridine

DME = 1,2-dimethoxyethane

DMF = dimethylformamide

DMSO = dimethylsulfoxide

EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

Et = ethyl

EtOAc = ethyl acetate

EtOH = ethanol

h = hour

HMDS = hexamethyldisilazane

HOAc = acetic acid

HOBt = 1-hydroxybenzotriazol

HPLC = high performance liquid chromatography

KHMDS = potassium bis(trimethylsilyl)amide

LDA = lithium diisopropylamide

Me = methyl

MeOH = methanol

min = minutes

PMB = 4-methoxybenzyl

Ph = phenyl

Pr = propyl

PyBOP = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

TEA = trietylamine

TFA = trifluoroacetic acid

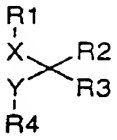
THF = tetrahydrofuran

TMSCN = trimethylsilyl cyanide

Tos = toluene-4-sulfonyl

CLAIMS

1. A compound of general Formula I



(I)

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R_1 represents,

C_1-C_6 alkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

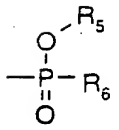
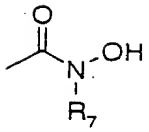
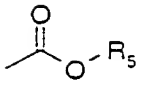
heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

or aryl, substituted with one or more basic groups such as amino, amidino and/or guanidino,

R_2 represents H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, Z_2N-CO-O-, ZO-CO-NZ- or Z_2N-CO-NZ- group,

R_3 represents $COOR_5$, $SO(OR_5)$, SO_3R_5, $P{=}O(OR_5)_2$, $B(OR_5)_2$, $P{=}OR_5(OR_5)$, or tetrazole, or any carboxylic acid isostere,

R_4 represents a  -group, or a  -group, or a  -group,

roup,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_6 represents C_1-C_6 alkyl, aryl, cycloalkyl, heterocyclyl, or an optionally N-substituted

H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group,

R_7 represents H or C_1-C_6 alkyl,

X represents O, S, SO, SO_2, $C(Z)_2$, N(Z), NR_7SO_2, SO_2NR_7, NR_7CO or $CONR_7$,

Y represents O, N(Z), S, $C(Z)_2$, or a single bond,

Z represents independently H, C_1-C_6 alkyl, aryl, cycloalkyl or heterocyclyl,

with the proviso that when X represents O, S, SO, SO_2, N(Z), NR_7SO_2, SO_2NR_7, or NR_7CO then Y represents $C(Z)_2$ or a single bond.

2. The compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R_1 represents,

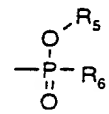
cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

R_2 represents H, C_1-C_3 alkyl, amino, halogen, hydroxy,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_6 represents C_1-C_6 alkyl, aryl, cycloalkyl, heterocyclyl, or an optionally N-substituted H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group,

X represents $C(Z)_2$,

Y represents O or $C(Z)_2$,

Z represents independently H or C_1-C_6 alkyl.

3. The compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R_1 represents,

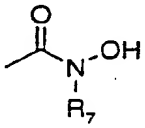
cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

R_2 represents H, C_1-C_3 alkyl, amino, halogen or hydroxy,

R_3 represents $COOR_5$,

R_4 represents a  -group,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_7 represents H or C_1-C_6 alkyl,

X represents $C(Z)_2$,

Y represents $C(Z)_2$, or a single bond,

Z represents independently H or C_1-C_6 alkyl.

4. The compound according to claim 1, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt,

wherein

R_1 represents,

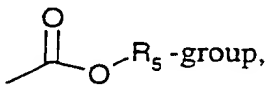
cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom:

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

R_2 represents H, C_1-C_3 alkyl, amino, halogen or hydroxy,

R_3 represents $COOR_5$,

R_4 represents a  -group,

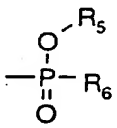
R_5 represents H, C_1-C_6 alkyl or aryl,

X represents $C(Z)_2$,

Y represents $C(Z)_2$, or a single bond,

Z represents independently H or C_1-C_6 alkyl.

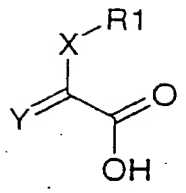
5. A process for the preparation of a compound according to any one of claims 1-4, wherein R_1, R_5, R_6, and Z are as defined in claim 1 and R_2 is H, R_3 is $COOR_5$,

R_4 represents a  -group,

X is $C(Z)_2$, Y is $C(Z)_2$,

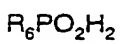
comprising the step of:

reacting a compound of Formula VI,



(VI)

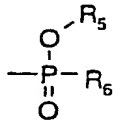
wherein R_1 and Z is as defined in claim 1 and X is $C(Z)_2$ and Y is $C(Z)_2$ with a compound of Formula IX,



(IX)

wherein R_6 is as defined in claim 1, in the presence of a suitable reagent, such as BSA or HMDS, under standard conditions.

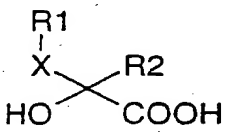
6. A process for the preparation of a compound according to any one of claims 1-4, wherein R_1, R_2, R_5, R_6 and Z are as defined in claim 1, R_3 is $COOR_5$, X is $C(Z)_2$, Y is O,

R_4 represents a  -group,

and

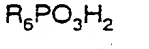
comprising the step of:

reacting a compound of Formula XII,



(XII)

wherein R_1 and R_2 are as defined in claim 1 and X is $C(Z)_2$ with a compound of Formula XIII,

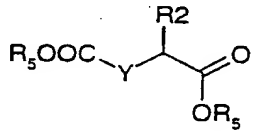


(XIII)

wherein R_6 is as defined in claim 1, in the presence of suitable coupling reagents such a DCC/DMAP, PyBop/DIPEA or $SOCl_2$, under standard conditions.

7. A process for the preparation of a compound according to any one of claims 1-4, wherein R_1 and R_2 are as defined in claim 1 and X and Y is $C(Z)_2$ or a single bond and R_3 and R_4 are $COOR_5$, comprising the step of:

reacting a compound of Formula XIV,



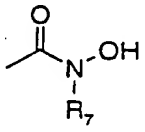
(XIV)

wherein R_2 and R_5 are as defined in claim 1 and Y is $C(Z)_2$ or a single bond, with a compound of the general Formula III,

$$R1—X—L \qquad (III)$$

wherein R_1 is as defined in claim 1, X is $C(Z)_2$ and L is a suitable leaving group, such as Cl, Br, I or tosyl, in the presence of a suitable base, such as LDA or NaH, under standard conditions.

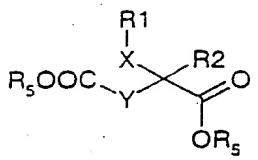
8. A process for the preparation of a compound according to any one of claims 1-4, wherein R_1, R_2, R_5, R_7, X, Y and Z are as defined in claim 1, R_3 is $COOR_5$ and

R_4 represents a 

-group,

comprising the step of:

reacting a compound of Formula XV,



(XV)

with a compound of Formula XVI,

$$HR_7NOH \qquad (XVI)$$

wherein R_7 is as defined in claim 1, in the presence of suitable reagents, such as DCC/DMAP, under standard conditions.

9. A pharmaceutical formulation containing a compound according to any one of claims 1-4 as active ingredient in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. The use of a compound according to any one of claims 1 to 4 in therapy.

11. The use of a compound according to any one of claims 1 to 4 for the manufacture of a medicament for the inhibition of carboxypeptidase U.

12. A method for treatment or prophylaxis of conditions associated with inhibition of carboxypeptidase U, comprising administering to a mammal, including man, in need of such treatment an effective amount of a compound as defined in any of claims 1-4.

13. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions associated with inhibition of carboxypeptidase U, comprising a compound as defined in any one of claims 1-4 in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A pharmaceutical formulation, comprising:

(i) a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, and

(ii) one or more antithrombotic agent with a different mechanism of action, such as an antiplatelet agent, thromboxane receptor inhibitor, synthetase inhibitor, fibrinogen receptor antagonist, prostacyclin mimetic, phosphodiesterase inhibitor or ADP-receptor (P_2T) antagonist,

in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

15. A kit of parts comprising:

(i) a pharmaceutical formulation containing a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and

(ii) a pharmaceutical formulation containing one or more antithrombotic agent with a different mechanism of action, such as an antiplatelet agent, thromboxane receptor inhibitor, synthetase inhibitor, fibrinogen receptor antagonist, prostacyclin mimetic, phosphodiesterase inhibitor or ADP-receptor (P_2T) antagonist, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier;

which compound (i) and agent (ii) are each provided in a form that is suitable for administration in conjunction with the other.

16. A method for treatment of a patient suffering from, or susceptible to, a condition in which inhibition of carboxypeptidase U and a different antithrombotic mechanism are required or desired, which method comprises administering to the patient a therapeutically effective total amount of

(i) a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; in conjunction with

(ii) one or more antithrombotic agent with a different mechanism of action, such as an antiplatelet agent, thromboxane receptor inhibitor, synthetase inhibitor, fibrinogen receptor antagonist, prostacyclin mimetic, phosphodiesterase inhibitor or ADP-receptor (P_2T) antagonist,

in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

17. A method for treatment of a patient suffering from, or susceptible to, a condition in which inhibition of carboxypeptidase U and a different antithrombotic mechanism are required or desired, which method comprises administering to the patient a formulation as defined in claim 15.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/00846

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 9/38, C07D 213/54, C07D 211/34, A61K 31/662, A61K 31/44, A61K 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" erlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2000	28 -08- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Göran Karlsson/gh Telephone No. + 46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/00846

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-17
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1

2. ☒ Claims Nos.: 1-15
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
pct/SE00/00846

The present claims 1-15 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. No special search effort can be made for searching unduly wide and speculative claims (PCT Search Guidelines C-III 3.7).

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts related to the compounds prepared in the examples.

The applicants attention is drawn to the fact that claims relating to inventions in which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report during any Chapter II procedure.